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DUSP protein phosphatases modulates the development of dilated cardiomyopathy

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Abstract

Hypertension, diabetes, and myocardial infarction are amongst the diverse pathological conditions known to aggravate heart dysfunction. As a compensatory response to stress, multiple signaling pathways like the mitogen-activated protein kinase (MAPK) cascades are activated in the heart. Because the p38 MAPK functions as a cardiac negative inotrope, we hypothesized that the phosphatases regulating its actions might also alter myocardial contractility. The role of the dual-specificity phosphatase (DUSP) proteins, some of which were previously shown to dephosphorylate p38 MAPK and inactivate it, still had to be characterized in the heart. We demonstrated that DUSP1 and DUSP4 are cardioprotective factors playing a critical role in the preservation of heart function. In fact, mice lacking both DUSP1 and DUSP4 (DUSP1/4-KO) displayed significantly reduced myocardial contractility, and developed spontaneously dilated cardiomyopathy with aging. Moreover, the chronic administration of a p38 MAPK pharmacologic inhibitor prevented the development of dilated cardiomyopathy in DUSP1/4-KO mice. Whether DUSP1 and DUSP4 are the only two primary regulators of p38 MAPK in the heart still has to be proven.

Biography

Mannix Auger-Messier is a pharmacologist (PhD from the University of Sherbrooke, 2005) and a molecular cardiovascular biologist (postdoctoral fellowship in Jeffery D. Molkentin's lab, HHMI, Cincinnati). He is a research professor at the Faculty of Medicine and Health Sciences - University of Sherbrooke (Division of Cardiology) since 2011. His research program aims to delineate cell signaling mechanisms participating in heart physiology and disease. His laboratory exploits a wide range of approaches from molecular pharmacology to physiopathology studies of the heart in genetically modified mouse models. Ongoing studies in his laboratory focus on elucidating the mechanisms of action of p38-MAPK and DUSP proteins in the heart. The Auger-Messier laboratory is currently funded by the Natural Sciences and Engineering Research Council of Canada (NSERC; 2013-2018) and the Canadian Institutes of Health Research (CIHR; 2013-2017).